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TOWNSEND AND TOWNSEND AND CREW, LLP			POPA, ILEANA	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/733,893

Applicant(s)

GERMAN ET AL.

Examiner

Ileana Popa

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Applicants' amendments to the claims of 12/11/2003 are acknowledged. Claims 1-30 are canceled. New claims 31-34 are added. No new matter is added by these claims.

Claims 31-34 are pending.

Note: Change in Art Unit and SPE

The examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. The information regarding the SPE and Art Unit is at the end of the Action.

Double patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 31, 33 and 34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 5, and 9 of

U.S. Patent No. 5,885,971. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants.

The instant claims 31, 33 and 34 are drawn to a method of delivering a protein to the bloodstream of a mammal comprising: introducing intraductally a naked DNA construct into a secretory gland cell, wherein the DNA construct comprises a DNA sequence of interest encoding for a secreted protein, wherein the sequence of interest is operably linked to a promoter, and wherein the protein encoded by the introduced DNA construct is produced in a secretory gland cell and the protein is delivered into the bloodstream of the mammal (claim 31). The mammal is a human, the protein is a human protein (claim 33), i.e., a growth hormone (claim 34). The instant claims embrace the following embodiments: delivery into the bloodstream of a mammal via a secretory gland of a secreted protein encoded by a naked DNA construct containing a promoter (claim 31), wherein the secreted protein is growth hormone (claim 34), and the delivery of DNA construct is into the lumen of the secretory gland duct (claim 31).

The patented claims recites a method of delivering a protein to the bloodstream of a mammal, comprising introducing a DNA construct into a salivary gland cell *in vivo*, wherein the DNA construct comprises a DNA sequence of interest which encodes a protein and a eukaryotic promoter sequence operably linked to the DNA sequence of interest, wherein the introduced DNA construct is expressed and the protein encoded by it is delivered to the bloodstream of the mammal (claim 1). The mammal is a human and the protein is a human protein (claim 3), delivery of the DNA construct is by introducing it into the lumen of a salivary gland duct (claim 5) and the protein is growth

hormone (claim 9). With respect to the limitation of the naked DNA construct, the specification defines that the DNA of interest can be naked (column 17, line 31). With respect to the limitation of intraductally delivery into a secretory gland, the salivary gland, as recited in patented claim 5, is a specific embodiment of secretory gland, therefore anticipates the genus of "secretory gland" recited in the instant claim 31. Therefore, the patented claims 1, 3, 5, and 9 anticipate claims 31, 33 and 34 of the instant application. Since the patent claims embrace all the limitation of the instant claims, the patent claims and the application claims are obvious variants of one another.

4. Claims 31-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of U.S. Patent No. 6,004,944. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants.

The instant claim 31-34 are drawn to a method of delivering a protein to the bloodstream of a mammal comprising: introducing intraductally a naked DNA construct into a secretory gland cell, wherein the DNA construct comprises a DNA sequence of interest encoding for a secreted protein, wherein the sequence of interest is operably linked to a promoter, and wherein the protein encoded by the introduced DNA construct is produced in a secretory gland cell and the protein is delivered into the bloodstream of the mammal (claim 31). The mammal is a human, the protein is a human protein (claim 33), i.e., a growth hormone (claim 34), and the secretory gland is liver (claim 32). The instant claims embrace the following embodiments: delivery into the bloodstream of a

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mammal via a secretory gland of a secreted protein encoded by a naked DNA construct containing a promoter (claim 31), wherein the secreted protein is growth hormone (claim 34), and the delivery of DNA construct is into the lumen of the liver duct (claims 31 and 32).

The patented claims recites a method of delivering a desired polypeptide to the bloodstream of a mammal, comprising introducing *in vivo* into the lumen of a salivary gland and into the lumen of the liver, of a construct comprising a DNA of interest that encodes a desired polypeptide and a promoter sequence operably linked to the DNA of interest, wherein the introduced DNA construct is expressed and the protein encoded by it is delivered to the bloodstream of the mammal from each the salivary gland and the liver (claim 6). With respect to the limitation of the mammal being a human, the specification defines that by mammal is meant any mammal to which intravenous protein delivery is desired, including humans (column 6, lines 49-50). With respect to the limitation of the naked DNA construct, the specification defines that the DNA of interest can be naked (column 12, lines 30-35). With respect to the limitation of a secreted human protein, wherein the protein is growth hormone, the specification defines that the proteins encoded by the DNA of interest are secreted proteins such as growth hormone (column 10, Table 1). With respect to the limitation of intraductally delivery into a salivary gland and the liver, the specifications defines that concurrent transformation of the secretory glands can be carried out several days apart (column 16, lines 42 and 43), i.e., intraductal administration of the DNA of interest into the liver can occur by itself. Therefore, the patented claim 6 anticipates claims 31-34 of the

instant application. Since the patent claims embrace all the limitation of the instant claims, the patent claims and the application claims are obvious variants of one another.

5. Claims 31, 33 and 34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 7 and 8 of U.S. Patent No. 6,255,289. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants.

The instant claims 31, 33 and 34 are drawn to a method of delivering a protein to the bloodstream of a mammal comprising: introducing intraductally a naked DNA construct into a secretory gland cell, wherein the DNA construct comprises a DNA sequence of interest encoding for a secreted protein, wherein the sequence of interest is operably linked to a promoter, and wherein the protein encoded by the introduced DNA construct is produced in a secretory gland cell and the protein is delivered into the bloodstream of the mammal (claim 31). The mammal is a human, the protein is a human protein (claim 33), i.e., a growth hormone (claim 34). The instant claims embrace the following embodiments: delivery into the bloodstream of a mammal via a secretory gland of a secreted protein encoded by a naked DNA construct containing a promoter (claim 31), wherein the secreted protein is growth hormone (claim 34), and the delivery of DNA construct is into the lumen of the secretory gland duct (claim 31).

The patented claims recites a method of delivering a protein to the bloodstream of a mammal, comprising introducing a DNA construct into the lumen of a pancreatic duct, wherein the DNA construct comprises a DNA sequence of interest which encodes

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a protein and a eukaryotic promoter sequence operably linked to the DNA sequence of interest, wherein the introduced DNA construct is expressed and the protein encoded by it is delivered to the bloodstream of the mammal (claim 1). The mammal is a human and the protein is a human protein (claim 7), and the protein is human growth hormone (claims 4 and 8). With respect to the limitation of the naked DNA construct, the specification defines that the DNA of interest can be naked (column 16, line 48). With respect to the limitation of intraductally delivery into a secretory gland, the pancreas, as recited in patented claim 1, is a specific embodiment of secretory gland, therefore anticipates the genus of "secretory gland" recited in the instant claim 31. Therefore, the patented claims 1, 2, 4, 7 and 8 anticipate claims 31, 33 and 34 of the instant application. Since the patent claims embrace all the limitation of the instant claims, the patent claims and the application claims are obvious variants of one another.

6. Claims 31-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,531,455. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants.

The instant claims 31-34 are drawn to a method of delivering a protein to the bloodstream of a mammal comprising: introducing intraductally a naked DNA construct into a secretory gland cell, wherein the DNA construct comprises a DNA sequence of interest encoding for a secreted protein, wherein the sequence of interest is operably linked to a promoter, and wherein the protein encoded by the introduced DNA construct

is produced in a secretory gland cell and the protein is delivered into the bloodstream of the mammal (claim 31). The secretory gland is liver (claim 32), the mammal is a human, the protein is a human protein (claim 33), i.e., a growth hormone (claim 34). The instant claims embrace the following embodiments: delivery into the bloodstream of a mammal via a secretory gland of a secreted protein encoded by a naked DNA construct containing a promoter (claim 31), wherein the secreted protein is growth hormone (claim 34), and the delivery of DNA construct is into the lumen of the liver duct (claims 31 and 32).

The patented claims recites a method of delivering a protein to the bloodstream of a mammal, comprising introducing a naked DNA construct into the lumen of a liver duct, wherein the DNA construct comprises a DNA sequence of interest which encodes a protein and a eukaryotic promoter sequence operably linked to the DNA sequence of interest, wherein the introduced DNA construct is expressed and the protein encoded by it is delivered to the bloodstream of the mammal (claim 1). The mammal is a human and the protein is a human protein (claim 2). With respect to the limitation of the secreted human protein being growth hormone, the specification defines the human growth hormone as an exemplary protein for expression and secretion by secretory glands (column 11, Table 1). Therefore, the patented claims 1, 2, 4, 7 and 8 anticipate claims 31, 33 and 34 of the instant application. Since the patent claims embrace all the limitation of the instant claims, the patent claims and the application claims are obvious variants of one another.

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7. Claims 31-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, and 5 of U.S. Patent No. 6,566,342. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are obvious variants.

The instant claims 31-34 are drawn to a method of delivering a protein to the bloodstream of a mammal comprising: introducing intraductally a naked DNA construct into a secretory gland cell, wherein the DNA construct comprises a DNA sequence of interest encoding for a secreted protein, wherein the sequence of interest is operably linked to a promoter, and wherein the protein encoded by the introduced DNA construct is produced in a secretory gland cell and the protein is delivered into the bloodstream of the mammal (claim 31). The secretory gland is liver (claim 32), the mammal is a human, the protein is a human protein (claim 33), i.e., a growth hormone (claim 34). The instant claims embrace the following embodiments: delivery into the bloodstream of a mammal via a secretory gland of a secreted protein encoded by a naked DNA construct containing a promoter (claim 31), wherein the secreted protein is growth hormone (claim 34), and the delivery of DNA construct is into the lumen of the liver duct (claims 31 and 32).

The patented claims recites a method of delivering a protein to the bloodstream of a mammal, comprising introducing a naked DNA construct into the lumen of a liver duct, wherein the DNA construct comprises a DNA sequence of interest which encodes a protein and a promoter sequence operably linked to the DNA sequence of interest, wherein the introduced DNA construct is expressed and the protein encoded by it is

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delivered to the bloodstream of the mammal (claim 1). The mammal is a human and the protein is a human protein (claim 2), i.e., growth hormone (claim 4). Therefore, the patented claims 1, 2, 4, 7 and 8 anticipate claims 31, 33 and 34 of the instant application. Since the patent claims embrace all the limitation of the instant claims, the patent claims and the application claims are obvious variants of one another.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hickman et al. (Human Gene Therapy, 1994, 5: 1477-1483), in view of Yang et al. (Proc. Natl. Acad. Sci. USA, 1993, 90: 4601-4605).

Hickman et al. teach gene delivery to the liver by direct injection of naked DNA construct into the liver lobes of rats or cats (page 1478, column 1, second paragraph). The naked DNA comprises a sequence encoding for a secreted protein, human α -1-antitrypsin; human α -1-antitrypsin is produced in the liver and appears in serum, i.e., is secreted into the blood (page 1480; column 2, second paragraph, and page 1481, column 2, second paragraph). Hickman et al. do not teach intraductal delivery or

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delivery to humans. Yang et al. teach intraductal delivery (Material and Methods, page 4603, column 1, second paragraph). Yang et al. teach that intraductal delivery results in efficient gene expression into hepatocytes (page 4603, column 1, second paragraph). Yang et al. also teach that intraductal delivery of therapeutic genes to the liver may be applied to humans (page 4603, column 2, Conclusions). Therefore, it would have been obvious to one of ordinary skills in the art, at the time the invention was made, to use the method of Hickman et al. to deliver gene of interest into the bloodstream of a mammal, using the intraductal delivery of Yang et al., with a reasonable expectation of success. The motivation to do so is provided by Yang et al., who teach that intraductal delivery is advantageous for human gene therapy, because it could be achieved by a nonsurgical approach, i.e., endoscopic retrograde cholangiography (page 4603, column 2, Conclusions). Thus, the claimed invention as a whole was prima facie obvious at the time the invention was made.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hickman et al. (Human Gene Therapy, 1994, 5: 1477-1483), taken with Yang et al. (Proc. Natl. Acad. Sci. USA, 1993, 90: 4601-4605), as applied to claims 31-33 above, and further in view of Heartlein et al. (Proc. Natl. Acad. Sci. USA, 1994, 91: 10967-10971).

Hickman et al. taken with Yang et al. do not teach growth hormone. Heartlein et al. teach delivery of human growth hormone *in vivo* (page 10967, column 2, second paragraph, page 10969, column 1, second paragraph, and page 10970, column 1, Discussion). Therefore, it would have been obvious to one of ordinary skills in the art,

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at the time the invention was made, to use intraductal gene delivery to the liver (see above) to produce the human growth hormone of Heartlein et al., with a reasonable expectation of success. The motivation to do so is provided by Heartlein et al., who teach that growth hormone deficiency may be treated by steady-state delivery of human growth hormone by gene therapy (page 10971, column 1, third paragraph). Thus, the claimed invention as a whole was prima facie obvious at the time the invention was made.

Conclusion

10. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546.

The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ileana Popa



DAVE TRONG NGUYEN
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